PATENT APPLICATION

THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE HONORABLE BOARD OF PATENT APPEALS AND

INTERFERENCES

In re the Application of: J. David Schaffer et al. Confirmation No.: 3848

Application No.: 10/597,767 Examiner: Pablo S. Whaley

Filed: August 7, 2006 Docket No.: 2004P00387WOUS
PHUS040120US3

For: GENOMIC ALGORITHMS FOR OPTIMIZATION OF
GENOMICS-BASED MEDICAL DIAGNOSTIC TESTS

BRIEF ON APPEAL

Appeal from Group 1631

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I. REAL PARTY IN INTEREST

The real party in interest for this appeal and the present application is Koninklijke Philips Electronics N.V., by way of an Assignment recorded in the U.S. Patent and Trademark Office at Reel 018063, Frame 0657.

II. RELATED APPEALS AND INTERFERENCES

There are no prior or pending appeals, interferences or judicial proceedings, known to Appellant, Appellant's representative, or the Assignee, that may be related to, or which will directly affect or be directly affected by or have a bearing upon the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 1-24 and 26 are pending.

Claims 3, 4, 7, 8, 22, and 23 are withdrawn.

Claim 25 is canceled.

Claims 1, 2, 5, 6, 9-21, 24, and 26 are rejected.

Claims 1, 2, 5, 6, 9-21, 24, and 26 are on appeal.

IV. STATUS OF AMENDMENTS

An Amendment B was filed after final on June 6, 2011 subsequent to the April 5, 2011 mailing date of the Office Action which is under appeal (hereinafter the "Office Action" or the "Final Office Action"). Amendment B was not entered in an Advisory Action mailed July 8, 2011.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The invention of **claim 1** is directed to a method for determining a classifier, the method comprising: producing a first generation chromosome population of chromosomes (page 4 lines 17-18; page 7 lines 13-17), each chromosome (70, 72) having (i) a set of genes specifying a sub-set of an associated set of measurements wherein each gene of the set of genes contains an index value which indexes a measurement of the associated set of measurements (page 4 lines 19-20; page 7 lines 11-13) and (ii) an expressed sub-set-size gene (80) having a value distinguishing expressed and unexpressed genes of the set of genes of the chromosome (page 4 lines 20-21; page 9 lines 27-31); computationally genetically evolving the genes of the chromosomes (page 4 lines 21-22; page 11 line 27-page 14 line 29) including the expressed sub-set-size gene (page 4 lines 21-22; page 11 lines 21-26; page 14 line 30-page 15 line 21) respective to a fitness criterion (page 4 lines 22-23; page 8 lines 17-25; page 16 lines 10-15) evaluated without reference to unexpressed genes (page 4 lines 22-24; page 5 line 31-page 6 line 1) to produce successive generation chromosome populations (page 4 lines 23-24), the computational genetic evolving being performed by a computing system (8) (page 9 lines 6-15); and selecting a classifier that uses the sub-set of associated measurements specified by the expressed genes of a chromosome identified by the genetic evolving (page 4 lines 24-26).

The invention of **claim 13** is directed to a medical diagnostic test for determining whether a medical subject has a pathology of interest, the method comprising: classifying measurements of the medical subject using a medical

diagnostic classifier determined **by the method of claim 1** (page 5 lines 25-28; page 8 line 31-page 9 line 5) and implemented by a computer (8) (page 9 lines 6-15), wherein the associated set of measurements characterize concentrations of organic macromolecules (page 5 lines 28-29) and the fitness criterion indicates fitness of the sub-set of associated measurements specified by the expressed genes of each chromosome for classifying medical subjects into a positive group having the pathology of interest and a negative group not having the pathology of interest (page 8 lines 2-8; page 8 lines 9-12; page 9 lines 1-5).

The invention of **claim 15** is directed to a method for determining a classifier, the method comprising: producing a first generation chromosome population of chromosomes (page 4 lines 27-28; page 5 lines 12-13; page 7 lines 13-17), each chromosome (70, 72) having a selected number of genes specifying a sub-set of an associated set of measurements (page 4 lines 28-29; page 7 lines 11-13); computationally genetically evolving the genes of the chromosomes (page 4 line 30; page 11 line 27-page 14 line 29) using a computing system (8) (page 9 lines 6-15) to produce successive generation chromosome populations (page 4 lines 30-31; page 5 lines 15-16); and selecting a classifier that uses the sub-set of associated measurements specified by genes of a chromosome identified by the genetic evolving (page 5 lines 10-11; page 8 lines 26-30). The producing of each successor generation chromosome population includes: generating offspring chromosomes from parent chromosomes of the present chromosome population by (i) filling genes of the offspring chromosome with gene values common to both parent chromosomes (page 12 lines 22-24) and (ii) filling remaining genes with gene values that are unique to one or the other of the parent chromosomes (page 4 line 31-page 5 line 5;

page 13 lines 24-27); selectively mutating genes values of the offspring chromosomes that are unique to one or the other of the parent chromosomes without mutating gene values of the offspring chromosomes that are common to both parent chromosomes (page 5 lines 5-7; page 12 lines 4-5; page 13 line 31-page 14 line 5); and updating the chromosome population with offspring chromosomes based on a fitness of each chromosome determined using the sub-set of associated measurements specified by genes of that chromosome (page 5 lines 7-10).

The invention of **claim 16** is directed to the method **of claim 15**, wherein a mutation rate for the selective mutating of the gene values that are unique to one or the other of the parent chromosomes is greater than 5% (page 14 lines 11-14).

The invention of **claim 18** is directed to a medical diagnostic test for determining whether a medical subject has a pathology of interest, the method comprising: classifying measurements of the medical subject using a medical diagnostic classifier determined **by the method of claim 15** (page 5 lines 25-28; page 8 line 31-page 9 line 5) and implemented by a computer (8) (page 9 lines 6-15), wherein the associated set of measurements characterize concentrations of organic macromolecules (page 5 lines 28-29) and the fitness quantifies effectiveness of the sub-set of associated measurements specified by genes of each chromosome for classifying a medical subjects into a positive group having the pathology of interest and a negative group not having the pathology of interest (page 8 lines 2-8; page 8 lines 9-12; page 9 lines 1-5).

The invention of **claim 19** is directed to a method for determining a classifier, the method comprising: producing a first generation chromosome population of chromosomes (page 5 lines 12-13; page 5 lines 12-13; page 7 lines 13-17), each chromosome (70, 72) having a selected number of genes specifying a sub-set of an associated set of measurements (page 5 lines 13-14; page 7 lines 11-13); computationally genetically evolving the genes of the chromosomes (page 5 line 15; page 11 line 27-page 14 line 29) to produce successive generation chromosome populations (page 5 lines 15-16; page 5 lines 15-16); and selecting a classifier that uses the sub-set of associated measurements specified by genes of a chromosome identified by the genetic evolving (page 5 lines 23-24; page 8 lines 26-30). The producing of each successor generation chromosome population includes: introducing a selected level of simulated noise into values of the set of measurements for a group of subjects (page 5 lines 16-18); generating offspring chromosomes by mating chromosomes of the present chromosome population (page 5 lines 18-19); selectively mutating genes of the offspring chromosomes (page 5 lines 19-20); and updating the chromosome population with offspring chromosomes based on a fitness of each chromosome determined respective to the values of the measurements of the group of subjects with the introduced simulated noise (page 5 lines 20-23; page 18 lines 8-32). The computational genetic evolving and the selecting are performed by a computing system (8) (page 9 lines 6-15).

The invention of **claim 20** is directed to a medical diagnostic test for determining whether a medical subject has a pathology of interest, the method comprising: classifying measurements of the medical subject using a medical diagnostic classifier determined **by the method of claim 19** (page 5 lines 25-28;

page 8 line 31-page 9 line 5) and implemented by a computer (8) (page 9 lines 6-15), wherein the associated set of measurements characterize concentrations of organic macromolecules (page 5 lines 28-29) and the fitness quantifies effectiveness of the sub-set of associated measurements specified by genes of each chromosome for classifying medical subjects into a positive group having the pathology of interest and a negative group not having the pathology of interest (page 8 lines 2-8; page 8 lines 9-12; page 9 lines 1-5).

The invention of **claim 21** is directed to a genetic optimization method comprising: computationally genetically evolving the genes of a chromosome population (page 5 line 30-page 6 line 1); and selecting an optimized chromosome produced by the genetic evolving (page 6 line 2). The evolving includes: evolving a number of expressed genes in each chromosome (page 5 lines 31-32) and employing a fitness criterion evaluated without reference to unexpressed genes of each chromosome (page 5 line 32-page 6 line 1); and selecting chromosomes that survive into each successive generation using a selection criterion biased toward selecting chromosomes having a smaller number of expressed genes over chromosomes having a larger number of expressed genes (page 12 lines 7-11; page 15 lines 22-26). The computational genetic evolving and the selecting are performed by a computing system (8) (page 9 lines 6-15).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Review of the following grounds of rejection in this case is earnestly requested:

Whether **claims 1, 2, 5, 6, 9, 10, 13, 14, 15, 17-21, and 24** are properly rejected under 35 U.S.C. § 103(a) as unpatentable over over Ooi et al., Bioinformatics vol. 19 no. 1 pp. 37-44 (2003) (hereinafter "Ooi") in view of Chtioui et al., J. Sci. Food Agric. (1998) (hereinafter "Chtioui"); and

Whether **claims 11, 12, and 26** are properly rejected under 35 U.S.C. § 103(a) as unpatentable over Ooi in view of Chtioui in further view of Liu et al., Evolutionary Computation, 12-17 May, pp. 297-302 (2002) (hereinafter "Liu").

VI. ARGUMENT

A. Claims 1, 2, 5, 6, 9, 10, 13, 14, 15, 17-21, and 24 distinguish patentably over the proposed combination of Ooi and Chtioui.

Claim 1 recites a method for determining a classifier, the method comprising: producing a first generation chromosome population of chromosomes, each chromosome having (i) a set of genes specifying a sub-set of an associated set of measurements wherein each gene of the set of genes contains an index value which indexes a measurement of the associated set of measurements and *(ii) an expressed sub-set-size gene having a value distinguishing expressed and unexpressed genes of the set of genes of the chromosome*; computationally genetically evolving the genes of the chromosomes *including the expressed sub-set-size gene* respective to a fitness criterion evaluated without reference to unexpressed genes to produce successive generation chromosome populations, the computational genetic evolving being performed by a computing system; and selecting a classifier that uses the sub-set of associated measurements specified by the expressed genes of a chromosome identified by the genetic evolving.

Claim 1 is rejected as allegedly obvious in view of the proposed combination of Ooi and Chtioui. Both claim 1 and the Ooi and Chtioui references relate to genetic algorithms for generating a classifier operating using a sub-set of available measurements. Ooi is directed to gene expression analysis (wherein the measurements characterize concentrations of organic macromolecules), while Chtioui is directed to object identification in artificial vision systems.

Ooi discloses chromosomes in which each gene contains an index value which indexes a measurement of the associated set of measurements. Ooi p. 39 1st column (heading "String Representation"). Each chromosome is represented by a string including an integer R specifying the size of the predictive set (corresponding to the expressed genes) and a set of genes $g_1,\ldots,g_{Rmax}$ of which the genes $g_1,\ldots,g_R$ are the expressed genes. Ooi page 39 1st column (heading "STRING

REPRESENTATION"). The gene pool is initialized to include *N* chromosomes, each represented by a string having a randomly selected predictive set size *R* in the range $[R_{min}, R_{max}]$ and a set of gene indices $g_1,\ldots,g_{Rmax}$. Ooi page 39 1st col. onto 2nd col. heading "Initialization and Evaluation". This gene pool is then evolved through the exchange of genetic information between pairs of parent chromosomes along with random mutation of genes. Ooi page 39 2nd column heading "Selection, Crossover, and Mutation".

In applying Ooi to claim 1, the final Office Action articulates:

> Ooi teaches genetic algorithms applied to the analysis of gene expression data. The genetic algorithm (GA) is based on the selection of the best individuals for reproduction. In particular, the process requires producing a chromosome string wherein each chromosome is associated with an ordered set of genes and a particular parameter (i.e. set of measurements); see page 39, Col. 1, ¶4, and Fig. 2. Therefore, the genes taught by Ooi are interpreted as sub-set-size genes since they occur in sets, and since the specification does not provide a limiting definition for "sub-set-size genes".
>
> Office Action page 7.

As best understood by Appellants, this articulation equates Ooi's set of gene indices $g_1,\ldots,g_{Rmax}$ with the recitation in claim 1 of "a set of genes specifying a sub-set of an associated set of measurements wherein each gene of the set of genes contains an index value which indexes a measurement of the associated set of measurements". Appellants do not disagree with this equivalence.

Appellants are unable to discern from the Office Action articulation what is being equated with the recitation in claim 1 of "an expressed sub-set-size gene having a value distinguishing expressed and unexpressed genes of the set of genes of the chromosome". Read literally, Ooi's genes "are interpreted as sub-set-size genes since they occur in sets, and since the specification does not provide a limiting definition of "sub-set-size genes". *Id.*

Respectfully, *claim 1* provides this limiting definition. An expressed sub-set-size gene is a *gene* which has a *value distinguishing expressed and unexpressed genes of the set of genes of the chromosome*. Ooi's genes $g_1,\ldots,g_{Rmax}$ do not distinguish expressed and unexpressed genes of the set of genes of the chromosome – rather, Ooi's genes $g_1,\ldots,g_{Rmax}$ are the set of genes of the chromosome.

Appellants respectfully submit that whether a gene of Ooi's chromosome is expressed or unexpressed is actually determined by the *predictive set size R*. Specifically, genes $g_1,\ldots,g_R$ are expressed, and genes $g_{R+1},\ldots,g_{Rmax}$ are unexpressed. *See* Ooi page 39 heading "String Representation" ("Only the first R genes out of the R_{max} genes included in the string are used for classification"). Thus, at most, one *might* equate Ooi's predictive set size R with the recitation in claim 1 of an expressed sub-set-size gene having a value distinguishing expressed and unexpressed genes of the set of genes of the chromosome.

However, claim 1 further recites computationally genetically evolving the genes of the chromosomes *including the expressed sub-set-size gene* respective to a fitness criterion evaluated without reference to unexpressed genes. There is no fair suggestion in Ooi that its computational genetic evolving includes evolving of the predictive set size R. In creating the *initial population* the value of R is stated to be randomly set to a value in the range $[R_{min}, R_{max}]$ for each chromosome. *See* Ooi page 39 heading "Initialization and Evaluation". Thereafter, Ooi's description of the computational genetic evolving (Ooi page 39 heading "Selection, Crossover and Mutation") does not mention evolving the predictive set size R.

Moreover, Ooi's described tests *do* fairly suggest that the predictive set size R is *not* computationally genetically evolved. In order to determine the best value for the predictive set size R, Ooi describes performing multiple runs with different values for the predictor size range $[R_{min}, R_{max}]$. Ooi pages 39-40 heading "Obtaining the Best Predictor Set for a Particular Set Size Range". Now consider: If the predictive set size R evolved, then the computational genetic evolving ought to optimize the predictive set size R, thus automatically yielding the best value for the predictive set size R. There would be no need for multiple runs with different values of $[R_{min}, R_{max}]$ (which, please recall, is the range from which R is randomly selected *when creating the initial population*).

The present application has the insight, as recited in claim 1, that one can optimize the expressed sub-set-size gene value by performing the computational genetic evolving of the genes of the chromosomes *including the expressed sub-set-size gene* respective to a fitness criterion evaluated without reference to unexpressed genes. This provides the advantage of "optimizing a classifier for a bioinformatic or other application without requiring *a priori* knowledge or selection of the number of measurements to be incorporated into the classifier." Present application page 6 lines 3-5.

Ooi does not disclose or fairly suggest this insight. Rather, Ooi performs calibration runs with different values for the initialization range $[R_{min}, R_{max}]$ in order to optimize its predictive set size R.

In responding to Appellants' remarks in Amendment A, the Office Action articulates:

> In response to applicant's arguments that Ooi and Chtioui do not teach expressed sub-set-size genes wherein each gene contains an index value indexing a measurement, Ooi teaches chromosomes associated with an ordered set of genes; see page 39, Col. 1, ¶4, and Fig. 2, which read on sub-set-size genes since they occur in sets. Furthermore, Ooi does not specifically teach genes containing index values which index a measurement of the associated sets of measurements, as in claims 1, 15, 19, and 21. However, Ooi suggests this limitation because the genes used in the process taught by Ooi are indexed; see, e.g. page 38, col. 2, ¶2, and page 39, col. 1, ¶5, and these index values are associated with frequency measurements and are used in expression profiles; see Figures 1 and 2. Therefore, Ooi makes obvious the use of genes with index values for indexing measurements.
>
> In response to applicant's arguments that Ooi does not teach adding an additional gene specifying R and evolving that added gene to optimize the number of features used in the classification, the claims do not recite these limitations. The claims do not recite any limitations related to the number of genes that can or cannot be evolved. The

claims require generating offspring chromosomes, but that does not appear to be the same as adding a gene.

Office Action pages 3-4.

Appellants do not understand how chromosomes associated with an ordered set of genes occurring in sets would read on sub-set-size genes. Each chromosome of Ooi does indeed comprise an ordered set of genes (or gene indexes, in Ooi's terminology) $g_1,\ldots,g_{Rmax}$. Appellants do not see how this discloses or even fairly suggests "an expressed sub-set-size gene having a value distinguishing expressed and unexpressed genes of the set of genes of the chromosome". Again, in Appellants' view what determines which of Ooi's genes $g_1,\ldots,g_{Rmax}$ are *expressed* (not merely *present* in the chromosome) is Ooi's predictive set size R (which, however, Ooi does not disclose or fairly suggest is evolved during the computational genetic evolving).

"Furthermore, Ooi does not specifically teach genes containing index values which index a measurement of the associated sets of measurements." Office Action page 3. Respectfully, Appellants actually *do* find this in Ooi. "[E]lements g_1, $g_2,\ldots,g_{Rmax}$ [are] the indices of a subset of genes picked from the truncated 1000 gene dataset." Ooi page 39 heading "String Representation".

Appellants are not sure how to respond to the second above-quoted paragraph. Ooi certainly teaches element R, although it is not referred to as a gene. Claim 1 does not recite R (again, that is Ooi's disclosure). Appellants agree that claim 1 does not recite any limitations as to the number of genes that can or cannot be *evolved*. Indeed, all genes of the chromosome may, in general, be subject to the *evolving*. But, claim 1 *does* recite evolving the expressed sub-set-size gene having a value distinguishing *expressed and unexpressed* genes, and further recites selecting a classifier that uses the sub-set of associated measurements *specified by the expressed genes* of a chromosome identified by the genetic evolving. Those expressed genes are distinguished by the *evolved* expressed sub-set-size gene, and so claim 1 *does* recite limitations pertaining to evolving the (expressed sub-set-size) gene to optimize the number of features used in the classification.

The Office Action does not allege that Chtioui discloses or fairly suggests an expressed sub-set-size gene (much less performing the computational genetic evolving of the genes of the chromosomes *including the expressed sub-set-size gene*). *See* Office Action page 4 ("In response to applicant's arguments that Chtioui does not teach sub-set-size genes wherein each gene contains an index value indexing a measurement, Ooi was relied upon for this teaching").

Chtioui (like the present application and like Ooi) discloses genetic algorithms. However, Chtioui discloses a very different approach. In the approach of Chtioui, chromosomes comprise *binary* genes, in which a value of 1 for the binary gene selects the corresponding feature (and, presumably, 0 indicates the corresponding feature is not selected). Chtioui p. 79 right column bottom section. The size of each chromosome is thus equal to the number of available features. *Id.* Appellants agree with the Office Action that there is no analog in Chtioui to the expressed sub-set-size *gene* of claim 1, or even to the predictive set size *R* of the genes of Ooi.

In view of the foregoing, it is respectfully submitted that the Examiner has not established *prima facie* obviousness of claim 1, and Appellants urge that the rejection of claim 1 be reversed.

Claim 15 recites (among other elements) generating offspring chromosomes from parent chromosomes of the present chromosome population by (i) filling genes of the offspring chromosome with gene values common to both parent chromosomes and (ii) filling remaining genes with gene values that are unique to one or the other of the parent chromosomes; selectively mutating genes values of the offspring chromosomes that are unique to one or the other of the parent chromosomes without mutating gene values of the offspring chromosomes that are common to both parent chromosomes; and updating the chromosome population with offspring chromosomes based on a fitness of each chromosome determined using the sub-set of associated measurements specified by genes of that chromosome.

Neither the initial Office Action nor the final Office Action has identified these features in either Ooi or Chtioui. *See* Amendment B pages 10-11 (*not* entered). Appellants do not find this subject matter in either Ooi or Chtioui.[1]

Claim 16 depends from claim 15 and recites wherein a mutation rate for the selective mutating of the gene values that are unique to one or the other of the parent chromosomes is greater than 5%. The Office Action argues this would have been obvious since Ooi "predictably calculates mutation rates of genes up to 0.02%; see page 39, Col. 2, page 41, Col. 1, and Table 1." Office Action pages 10-11.[2]

Respectfully, Ooi does not "calculate" mutation rates of genes up to 0.02%. Rather, Ooi *performs experiments* with mutation rates (probabilities p_m) in the range

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[1] Appellants note that the Examiner addressed these limitations for the first time in the Advisory Action mailed July 8, 2011 (refusing entry of Amendment B). Although these arguments were presented after the close of prosecution, Appellants here reply to the comments presented in the Advisory Action for completeness. First, the Examiner argues that limitation (ii) is a conditional limitation. It is not – claim 2 affirmatively recites (ii) filling remaining genes with gene values that are unique to one or the other of the parent chromosomes. The Examiner may be proposing that in some instances there may be no "remaining genes". However, in that case the method of claim 15 would *not* be performed. (The Examiner's argument is akin to arguing that "welding a workpiece" is a conditional limitation because in some cases no workpiece may be available). Moreover, it should be noted that the situation of there being no "remaining genes" is a trivial case that would only occur if the gene pool is initialized with identical chromosomes; otherwise, there will always be at least two "remaining genes" during the first iteration. Appellants do not understand the Examiner's argument in the Advisory Action which seems to suggest that Ooi and Chtioui are configured such that there are *never* any remaining genes. In order fill *all* genes of the offspring chromosome with gene values common to both parent chromosomes, it is necessary that the two chromosomes be identical, in which case the offspring will be identical with the parents. Consider a simple example: parent 1 is abcde and parent 2 is abfde. Then the offspring chromosome includes common gene values a, b, d, e, and there are two remaining gene values (c and f) each unique to one parent. The operation (ii) would fill the last gene with either c or f.

[2] The Office Action does not expressly state that claim 16 stands rejected under 35 U.S.C. § 103(a) based on the proposed combination of Ooi and Chtioui, and even acknowledges that "Ooi does not teach a mutation rate for the selective mutating of the gene value that are unique to one or the other of the parent chromosomes that is greater than 5%, as in claim 16." Office Action page 9. However, claim 16 is listed as rejected in the Office Action Summary, and articulates alleged obviousness of mutation rates greater than 5% at pages 10-11 as cited herein. Accordingly, Appellants treat claim 16 herein as rejected under 35 U.S.C. § 103(a) based on the proposed combination of Ooi and Chtioui.

0.0005-0.02. The *lower* 5% threshold of claim 16 is *250 times larger* than the *uppermost* 0.02% rate of Ooi. Respectfully, the skilled artisan reading Ooi would find no motivation to test a mutation rate *250 times larger* than the *largest* mutation rate tested by Ooi. The Examiner's rationale appears to be that since the reference (Ooi) tested different mutation rates within one range, it would be obvious to test *any other* range, no matter how wildly different from the range tested by the reference.

Moreover, Ooi does not disclose or fairly suggest a mutation rate for the selective mutating of the gene values *that are unique to one or the other of the parent chromosomes* is greater than 5% in *combination* with *not* mutating gene values of the offspring chromosomes that are common to both parent chromosomes (as per base claim 15). Ooi does not fairly suggest using different mutation rates for common genes as compared with unique genes, much less the specific value and range set forth in claim 16.

The present application particularly points out that this is a *surprising* result:

> In some embodiments, a mutation rate for the unique gene values of greater than 5% has been found to be suitable. In some embodiments, a mutation rate for the unique gene values of around 15% has been found to be suitable. *By contrast, when both common and unique gene values are mutated selectively, mutation rates greater than 5% generally leads to poor convergence* characteristics far the genetic evolving.
>
> Present application page 14 lines 11-16 (italics and underscore added).

Accordingly, it is respectfully submitted that the Examiner has not established *prima facie* obviousness of claims 15 and 16, and Appellants urge that the rejections of claims 15 and 16 be reversed.

Claim 19 recites the producing of each successor generation chromosome population includes: *introducing a selected level of simulated noise into values of the set of measurements* for a group of subjects; generating offspring chromosomes by mating chromosomes of the present chromosome population; selectively mutating genes of the offspring chromosomes; and updating the chromosome population with offspring chromosomes based on a fitness of each chromosome determined respective to the values of the measurements of the group of subjects *with the introduced simulated noise*.

Claim 19 stands rejected as unpatentable over the proposed combination of Ooi and Chtioui. However, the Office Action expressly states:

> In response to applicant's argument regarding limitations directed to noise, Ooi and Chtioui *do not teach* introducing a selected level of noise into values of measurements of the measured subjects, as in claims 11, 19, and 26. However, Liu describes the addition of noise into measurement data at a number of different points; see page 297, Col. 2, as set forth below.
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> Office Action page 5 (italics added).

Whether Liu teaches addition of noise is irrelevant as pertaining to claim 19, because claim 19 is rejected based on Ooi and Chtioui alone.[3] *Nonetheless*, for completeness Appellants address the tertiary Liu reference here.

The paragraph of Liu addressing noise is reproduced below:

> DNA arrays yield a global view of gene expression and can be used in a number of interesting ways, such as gene clustering, tissue classifying, and regulatory network inferring, etc. Recent studies on molecular level classification of tissues have produced remarkable results, and indicated that gene expression assays could significantly

[3] Appellants pointed out in Amendment B (which was *not* entered as per Advisory Action mailed July 8, 2011) that if the Examiner believes that Lui is additionally required in order to properly reject claim 19, then the Examiner should withdraw finality and issue a new non-Office Action making that new rejection. The Advisory Action argues this was merely a clerical error and that rejection under the three-way combination of Ooi, Chtioui, *and Liu* was intended.

aid in the development of efficient cancer and classification platforms. However, classification based on the DNA array data is confronted with more challenges. One of the major challenges is the overwhelming number of genes relative to the number of training samples in the data sets. Many of the genes are not relevant to the distinction between different tissue and introduce **noise** in the classification process, and thus potentially drown out the contributions of the relevant ones. Moreover, for diagnostic purposes it is important to find small sets of genes those are sufficiently informative to distinguish between cells of different Another challenge is that the data often contain "technical" and "biological" **noises**. The "technical" **noise** can be introduced at a number of different stages, such as production of the DNA array, preparation of the samples, hybridization between cDNA and array, and signal analysis and extraction of the hybridization results. The "biological" **noise** can come from non-uniform genetic background of the samples being compared, or from the impurity or misclassification of tissue samples. It can be said that the choice of genes is the key of the molecular level classification, and should be paid more attention. This paper goes further in this direction and focuses on the topic of selecting a small subset of informative genes.

Liu page 297, paragraph spanning 1st→2nd columns (boldface and underscores on the word "noise" are added).

Respectfully, the skilled artisan reading the foregoing would ***not*** be motivated by Liu to introduce a selected level of simulated noise into values of the set of measurements for a group of subjects during the producing of each successor generation chromosome population. Rather, the skilled artisan would learn from Liu that irrelevant genes introduce noise that potentially drowns out relevant genes (in other words **noise is bad**), and that data often contain technical and biological noise that presents a challenge to the classification (in other words **noise is bad**).

Query: In what way would this disclosure of Liu *motivate* the skilled artisan to *introduce* a selected level of simulated noise into values of the set of measurements

for a group of subjects during the producing of each successor generation chromosome population? It would *not* so motivate. To the contrary, Liu would motivate the skilled artisan to assiduously *avoid* noise whenever and wherever possible, because Liu teaches that noise can drown out relevant genes and presents a challenge to the classification. In other words, Liu *teaches away* from claim 19.

On the other hand, the *present application* (not Liu) discloses:

> Introducing simulated noise reduces sensitivity of the genetic evolving to systematic measurement errors, but diminishes the tendency for the discovery algorithm to find weak patterns. For some bioinformatics measurement sets, it has been found that coefficients of variation (cv) greater than about 2% in the added simulated Gaussian noise prevents convergence to weak biologically significant patterns. Present application page 18 lines 28-32.

The present application (*not* Liu) provides motivation for introducing a selected level of simulated noise: doing so reduces sensitivity of the genetic evolving to systematic measurement errors. *Id.*

Accordingly, it is respectfully submitted that the Examiner has not established *prima facie* obviousness of claim 19, and Appellants urge that the rejection of claim 19 be reversed.

Claim 21 recites a genetic optimization method comprising computationally genetically evolving the genes of a chromosome population, and selecting an optimized chromosome produced by the genetic evolving, wherein the evolving includes evolving a number of expressed genes in each chromosome and employing a fitness criterion evaluated without reference to unexpressed genes of each chromosome; and *selecting chromosomes that survive into each successive generation using a selection criterion biased toward selecting chromosomes having a smaller number of expressed genes over chromosomes having a larger number of expressed genes.*

The Office Action does not identify the above italicized subject matter in Ooi, Chtioui, or their combination. Claim 21 is also a subject of the omnibus argument directed to claims 1, 15, 19, and 21, which does not address the italicized subject matter. Office Action pages 6-7. (Said another way, the Office Action nowhere alleges that either Ooi or Chtioui disclose or fairly suggest selecting chromosomes that survive into each successive generation *using a selection criterion biased toward selecting chromosomes having a smaller number of expressed genes over chromosomes having a larger number of expressed genes.*) Moreover, nothing in the Response to Arguments at pages 3-5 addresses the italicized subject matter.

In Amendment B (which was *not* entered), Appellants respectfully submitted that the Office should either identify where this recited limitation is found in Ooi and/or Chtioui, or withdraw the rejection and allow claim 21, or apply a new rejection in a new non-final Office Action that includes a reference addressing the foregoing limitation. Amendment B at page 12.

The Advisory Action mailed July 8, 2011 did not enter Amendment B, but did present an argument that the italicized subject matter is found in Ooi:

> In response to applicant's arguments on page 12 that the limitation for "selecting chromosomes that survive into each successive generation using a selection criteria biased toward selecting chromosomes having a smaller number of expressed genes over a larger number of expressed genes, Ooi teaches a selection process based on survival of the fittest (page 38, col. 1, 3), which inherently results in selecting a smaller number of expressed genes because it uses termination conditions. In addition, Ooi teaches that empty spots (i.e. unexpressed genes) on the microarray are excluded from the genetic evolution process; see page 38, Col. 2. Therefore, applicant's arguments are not persuasive because Ooi at a minimum suggests selection criteria that are biased towards selecting chromosomes having a smaller number of expressed genes.
>
> Advisory Action mailed July 8, 2011.

Having finally received an articulation from the United States Patent & Trademark Office explaining the rationale under which claim 21 is rejected, Appellants now respond as follows.

"Ooi teaches a selection process based on survival of the fittest (page 38, col. 1, 3), which inherently results in selecting a smaller number of expressed genes because it uses termination conditions". Respectfully, this statement is nonsensical. How does a process based on survival of the fittest *inherently* result in selecting a smaller number of expressed genes? The following qualitative example is illustrative. Assuming that the theory of (biological) evolution is correct, we can conclude that every species of animal or plant alive today is highly fit as it has survived to the present while most species have gone extinct. If a process based on survival of the fittest inherently results in selecting a smaller number of expressed genes, then every species alive today should have a *very* small number of expressed genes.

In actuality, each expressed gene provides an additional degree of "flexibility", and so a process based on survival of the fittest would instead be expected to tend to drive toward a *larger* number of expressed genes, as this would enable more "fine-tuning" to meet the fitness criterion which (as recited in claim 21) is evaluated without reference to unexpressed genes of each chromosome. However, as recognized in the present application (*not* Ooi), this can result in overfitting:

> With returning reference to FIGURE 1, the selection algorithm of the genetic algorithm is modified versus the Eshelman CHC algorithm to be biased to favor chromosomes having a smaller number of expressed genes. A smaller number of expressed genes corresponds to a smaller sub-set of measurements in the diagnostic test, and reduces the likelihood of overfitting the learning cases.
>
> Present application page 15 lines 22-26.

Regarding the "termination conditions" argument, Appellants do not see how the use of termination conditions in a survival of the fittest process inherently results in selecting a smaller number of expressed genes. Most iterative processes employ a

termination condition; otherwise they run forever. In the case of Ooi, the process of evaluation, crossover, and mating "are repeated for *G* generations." Ooi page 39 2nd column heading "Termination". Based on the examples in Ooi, it looks like *G* is generally a fixed value, such as *G*=100. *See* Ooi p. 40 2nd col. heading "RESULTS".

The Advisory Action does not explain why terminating after *G* iterations inherently results in selecting a smaller number of expressed genes.

"In addition, Ooi teaches that empty spots (i.e. unexpressed genes) on the microarray are excluded from the genetic evolution process; see page 38, Col. 2." Respectfully, those empty spots are not part of the chromosomes undergoing evolution, *and are not even part of the measured dataset*. All that passage of Ooi is stating is that the data are preprocessed *before* the genetic algorithm is applied to remove spots with missing data, control spots, and empty spots. That is why Ooi refers to it as *preprocessing*.

The key to supporting any rejection under § 103 is a clear articulation of the reason(s) why the claim would have been obvious. MPEP § 2142. Rejections on obviousness cannot be sustained with mere conclusory statements. *Id*. Rather, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. *Id*.

It it is respectfully submitted that the articulation of the rejection of claim 21 set forth in the Advisory Action does not meet this standard. Accordingly, the Examiner has not established *prima facie* obviousness of claim 21, and Appellants urge that the rejection of claim 21 be reversed.

B. Claims 11, 12, and 26 distinguish patentably over the proposed combination of Ooi, Chtioui, and Liu.

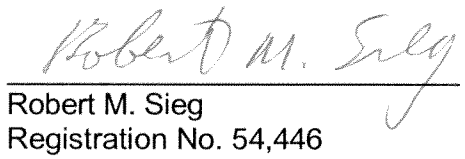
Claims 11 and 12 depend from claim 1. The Office Action does not allege that the deficiencies of Ooi and Chtioui respective to claim 1 as set forth in Section A herein are in any way remediated by Liu. Accordingly, it is respectfully submitted that the Examiner has not established *prima facie* obviousness of claims 11 and 12, and Appellants urge that the rejections of claims 11 and 12 be reversed.

Claim 26 depends from claim 21. Neither the Office Action nor the Advisory Action allege that the deficiencies of Ooi and Chtioui respective to claim 21 as set forth in Section A herein are in any way remediated by Liu. Accordingly, it is respectfully submitted that the Examiner has not established *prima facie* obviousness of claim 26, and Appellants urge that the rejections of claim 26 be reversed.

CONCLUSION

For all of the reasons discussed above, it is respectfully submitted that the rejections are in error and that claims 1, 2, 5, 6, 9-21, 24, and 26 are in condition for allowance. For all of the above reasons, Appellants respectfully request this Honorable Board to reverse the all pending rejections of the appealed claims.

Respectfully submitted,



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APPENDICES

VII. CLAIMS APPENDIX

Claims involved in the Appeal are as follows:

1. A method for determining a classifier, the method comprising:

producing a first generation chromosome population of chromosomes, each chromosome having (i) a set of genes specifying a sub-set of an associated set of measurements wherein each gene of the set of genes contains an index value which indexes a measurement of the associated set of measurements and (ii) an expressed sub-set-size gene having a value distinguishing expressed and unexpressed genes of the set of genes of the chromosome;

computationally genetically evolving the genes of the chromosomes including the expressed sub-set-size gene respective to a fitness criterion evaluated without reference to unexpressed genes to produce successive generation chromosome populations, the computational genetic evolving being performed by a computing system; and

selecting a classifier that uses the sub-set of associated measurements specified by the expressed genes of a chromosome identified by the genetic evolving.

2. The method as set forth in claim 1, wherein the set of genes of each chromosome define an ordered set of genes, and the expressed sub-set-size gene contains an ordinal position value separating the expressed and unexpressed genes in the ordered set.

3-4. (Withdrawn)

5. The method as set forth in claim 2, wherein the ordered set of genes has first and second ends with the gene closest to the first end being an expressed gene, and the genetic evolving includes:

generating offspring chromosomes, each offspring chromosome being generated from two parent chromosomes of the present chromosome population by: (i) filling genes of the offspring chromosome with gene values common to both parent chromosomes using the ordering of the common gene values in a selected one of the two parent chromosomes and biasing the filling toward the first end of the ordered set of genes of the offspring chromosome and (ii) filling remaining genes with gene values that are unique to one or other of the parent chromosomes.

6. The method as set forth in claim 5, wherein the filling of genes with gene values common to both parent chromosomes includes:

at least occasionally varying the ordering of the common gene values in the offspring chromosome from the ordering of the common gene values in the selected one of the two parent chromosomes.

7-8. (Withdrawn)

9. The method as set forth in claim 1, wherein the computational genetic evolving includes:

generating offspring chromosomes from selected combinations of chromosomes of the present generation chromosome population; and

replacing a selected chromosome of the present generation chromosome population with a selected offspring chromosome if either: (i) the selected offspring chromosome is more fit than the selected chromosome of the present generation chromosome population, or (ii) the selected offspring chromosome is as fit as the selected chromosome of the present generation chromosome population and the selected offspring chromosome has fewer expressed genes than the selected chromosome of the present generation chromosome population.

10. The method as set forth in claim 9, wherein:

the selected offspring chromosome is the most fit offspring chromosome and the selected chromosome of the present generation chromosome population is the least fit chromosome of the present generation chromosome population; and

the replacing is repeated until the most fit offspring chromosome is less fit than the least fit chromosome of the present generation chromosome population.

11. The method as set forth in claim 1, wherein the fitness criterion indicates the fitness of the sub-set of associated measurements specified by the expressed genes of each chromosome for classifying a group of measured subjects into two or more classifications, and the method further includes:

before producing of each successive generation chromosome population, introducing a selected level of simulated noise into values of measurements of the measured subjects.

12. The method as set forth in claim 1, wherein the fitness criterion indicates the fitness of the sub-set of associated measurements specified by the expressed

genes of each chromosome for classifying a group of measured subjects into two or more classifications, and the method further includes:

before producing of each successive generation chromosome population, randomly or pseudorandomly splitting a set of measured subjects into a training group and a test group.

13. A medical diagnostic test for determining whether a medical subject has a pathology of interest, the method comprising;

classifying measurements of the medical subject using a medical diagnostic classifier determined by the method of claim 1 and implemented by a computer, wherein the associated set of measurements characterize concentrations of organic macromolecules and the fitness criterion indicates fitness of the sub-set of associated measurements specified by the expressed genes of each chromosome for classifying medical subjects into a positive group having the pathology of interest and a negative group not having the pathology of interest.

14. The method as set forth in claim 13, wherein the associated set of measurements characterizing concentrations of organic macromolecules in a medical subject is one of:

a set of measurements of dots of a microarray processed using a biological sample taken from the medical subject, and

a set of signal levels of a mass spectrogram measured for a biological sample taken from the medical subject.

15. A method for determining a classifier, the method comprising:

producing a first generation chromosome population of chromosomes, each chromosome having a selected number of genes specifying a sub-set of an associated set of measurements;

computationally genetically evolving the genes of the chromosomes using a computing system to produce successive generation chromosome populations, the producing of each successor generation chromosome population including:

generating offspring chromosomes from parent chromosomes of the present chromosome population by: (i) filling genes of the offspring chromosome with gene values common to both parent chromosomes and (ii) filling remaining genes with gene values that are unique to one or the other of the parent chromosomes,

selectively mutating genes values of the offspring chromosomes that are unique to one or the other of the parent chromosomes without mutating gene values of the offspring chromosomes that are common to both parent chromosomes, and

updating the chromosome population with offspring chromosomes based on a fitness of each chromosome determined using the sub-set of associated measurements specified by genes of that chromosome; and

selecting a classifier that uses the sub-set of associated measurements specified by genes of a chromosome identified by the genetic evolving.

16. The method as set forth in claim 15, wherein a mutation rate for the selective mutating of the gene values that are unique to one or the other of the parent chromosomes is greater than 5%.

17. The method as set forth in claim 15, wherein only a sub-set of the genes of each chromosome are expressed genes and the fitness of each chromosome is determined using the sub-set of the associated measurements specified by the expressed genes of that chromosome.

18. A medical diagnostic test for determining whether a medical subject has a pathology of interest, the method comprising:

classifying measurements of the medical subject using a medical diagnostic classifier determined by the method of claim 15 and implemented by a computer, wherein the associated set of measurements characterize concentrations of organic macromolecules and the fitness quantifies effectiveness of the sub-set of associated measurements specified by genes of each chromosome for classifying a medical subjects into a positive group having the pathology of interest and a negative group not having the pathology of interest.

19. A method for determining a classifier, the method comprising:

producing a first generation chromosome population of chromosomes, each chromosome having a selected number of genes specifying a sub-set of an associated set of measurements;

computationally genetically evolving the genes of the chromosomes to produce successive generation chromosome populations, the producing of each successor generation chromosome population including:

introducing a selected level of simulated noise into values of the set of measurements for a group of subjects,

generating offspring chromosomes by mating chromosomes of the present chromosome population,

selectively mutating genes of the offspring chromosomes, and

updating the chromosome population with offspring chromosomes based on a fitness of each chromosome determined respective to the values of the measurements of the group of subjects with the introduced simulated noise; and

selecting a classifier that uses the sub-set of associated measurements specified by genes of a chromosome identified by the genetic evolving;

wherein the computational genetic evolving and the selecting are performed by a computing system.

20. A medical diagnostic test for determining whether a medical subject has a pathology of interest, the method comprising:

classifying measurements of the medical subject using a medical diagnostic classifier determined by the method of claim 19 and implemented by a computer, wherein the associated set of measurements characterize concentrations of organic macromolecules and the fitness quantifies effectiveness of the sub-set of associated measurements specified by genes of each chromosome for classifying medical

subjects into a positive group having the pathology of interest and a negative group not having the pathology of interest.

21. A genetic optimization method comprising:

computationally genetically evolving the genes of a chromosome population, the evolving including:

evolving a number of expressed genes in each chromosome and employing a fitness criterion evaluated without reference to unexpressed genes of each chromosome, and

selecting chromosomes that survive into each successive generation using a selection criterion biased toward selecting chromosomes having a smaller number of expressed genes over chromosomes having a larger number of expressed genes; and

selecting an optimized chromosome produced by the genetic evolving;

wherein the computational genetic evolving and the selecting are performed by a computing system.

22-23. (Withdrawn)

24. The method as set forth in claim 21, wherein the genetic evolving includes:

generating an offspring chromosome by mating two selected parent chromosomes of the present chromosome population; and

selectively mutating genes of the offspring chromosome that are unique to one or the other of the two parent chromosomes without mutating genes of the offspring chromosome that are common to both parent chromosomes.

25. (Canceled)

26. The method as set forth in claim 21, wherein the genetic evolving includes:

generating offspring chromosomes by mating selected parent chromosomes of the parent chromosome population and introducing a select level of simulated noise into measurement values associated with the parent chromosomes.

VIII. EVIDENCE APPENDIX

NONE

IX. RELATED PROCEEDINGS APPENDIX

NONE